Evidence that the DNA endonuclease ARTEMIS also has intrinsic 5'-exonuclease activity.

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Public Summary:
We were able to show that the nuclease Artemis can cut DNA from DNA ends as well as internally. This is relevant to the role of Artemis in the human immune system and in the repair of DNA damage that arises in all cells every day due to natural processes.

Scientific Abstract:
ARTEMIS is a member of the metallo-beta-lactamase protein family. ARTEMIS has endonuclease activity at DNA hairpins and at 5'- and 3'-DNA overhangs of duplex DNA, and this endonucleolytic activity is dependent upon DNA-PKcs. There has been uncertainty about whether ARTEMIS also has 5'-exonuclease activity on single-stranded DNA and 5'-overhangs, because this 5'-exonuclease is not dependent upon DNA-PKcs. Here, we show that the 5'-exonuclease and the endonuclease activities co-purify. Second, we show that a point mutant of ARTEMIS at a putative active site residue (H115A) markedly reduces both the endonuclease activity and the 5'-exonuclease activity. Third, divalent cation effects on the 5'-exonuclease and the endonuclease parallel one another. Fourth, both the endonuclease activity and 5'-exonuclease activity of ARTEMIS can be blocked in parallel by small molecule inhibitors, which do not block unrelated nucleases. We conclude that the 5'-exonuclease is intrinsic to ARTEMIS, making it relevant to the role of ARTEMIS in nonhomologous DNA end joining.